Structural studies on mechanosensory Filamin A domain modules

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Abstract

Filamins are cytoskeletal proteins initially discovered as potent actin filament cross-linkers that organize cortical actin into structured networks. In addition, filamins serve as a linker between extracellular matrix and cytoskeleton by binding cell surface receptors, such as integrins. Filamins also function as scaffolds for several signaling molecules and bind other cytoskeletal proteins known to regulate cell adhesion and dynamics. Recent findings have established the fact that filamins can respond to actomyosin network generated traction and function as cellular mechanosensors. Filamins are dimeric, elongated proteins where each subunit is made of an N terminal actin binding domain, followed by a string of altogether 24 immunoglobulin-like domains that function as interaction modules for other proteins. These domains are divided into two rods separated by flexible hinge region. While full filamin waits for detailed structural characterization, the C terminal rod 2 is well characterized. Earlier structural studies reveal that in rod 2 there are three tightly interacting pairs of domains, two of which in resting state hide protein binding sites. These sites can be mechanically exposed which provides molecular level mechanism for mechanosensation. Here, we report (1) the first co-crystal structure of a two-domain mechanosensor module of filamin A domains 20-21 in complex with peptide. The structure can be thought as the end-state model for the interacting protein binding to actomyosin network stretched filamin. We have also (2) solved the crystal structure of a three domain module of filamin A domains 3-5, which reveals novel type of domain-domain interactions in immunoglobulin superfamily and first evidence of potential mechanically regulated domain interactions in the N terminal rod 1 region of filamins.